NEW DRUG UPDATE – 1998/99

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NEW DRUG UPDATE

TROVAFLOXACIN MESYLATE TABLETS - ALATROFLOXACIN MESYLATE INJECTION - Trovan® Tablets and Trovan® I.V. by Pfizer Inc. - 1S

INDICATIONS: Trovafloxacin and alatrofloxacin are indicated for the treatment of infections listed in Table 1 when caused by susceptible strains of the designated microorganisms.

Table 1: FDA-Approved Indications for Trovafloxacin and Alatrofloxacin

Infection	Microorganism
Nosocomial pneumonia	*E. coli*, *P. aeruginosa*, *H. influenzae* or *S. aureus*
Community-acquired pneumonia	*S. pneumoniae*, *H. influenzae*, *K. pneumoniae*, *S. aureus*, *M. pneumoniae*, *M. catarrhalis*, *L. pneumophilia* or *C. pneumoniae*
Acute bacterial exacerbation of chronic bronchitis	*H. influenzae*, *M. Catarrhalis*, *S. pneumoniae*, *S. aureus* or *H. parainfluenzae*
Acute sinusitis	*H. influenzae*, *M. catarrhalis* or *S. pneumoniae*
Complicated intra-abdominal infections, including post-surgical infections	*E. coli*, *B. fragilis*, viridans group streptococci, *P. aeruginosa*, *K. pneumoniae*, *Peptostreptococcus* spp. or *Prevotella* spp.
Gynecologic and pelvic infections including endomyometritis, parametritis, septic abortion and postpartum infections	*E. coli*, *B. fragilis*, viridans group streptococci, *E. faecalis*, *S. agalactiae*, *Peptostreptococcus* spp., *Prevotella* spp. or *Gardnerella vaginalis*
Prophylaxis of infection associated with elective colorectal surgery, vaginal and abdominal hysterectomy	
Uncomplicated skin and skin structure infections	*S. aureus*, *S. pyogenes* or *S. agalactiae*
Complicated skin and skin structure infections, including diabetic foot infections	*S. aureus*, *S. agalactiae*, *P. aeruginosa*, *E. faecalis*, *E. coli* or *P. mirabilis*
Uncomplicated urinary tract infections	*E. coli*
Chronic bacterial prostatitis	*E. coli*, *E. faecalis* or *S. epidermidis*
Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females	*N. gonorrhoeae*
Cervicitis	*C. trachomatis*

CLINICAL PHARMACOLOGY: Trovafloxacin (CP 99,219) is a fluoroquinolone antibiotic with a broad spectrum of activity against gram-positive, gram-negative and anaerobic microorganisms. Alatrofloxacin is the L-alanyl-L-alanyl prodrug of trovafloxacin.

Trovafloxacin appears to be more potent and offer a broader spectrum of activity against gram-positive organisms than other previously available fluoroquinolones. In general, it has greater activity against gram-positive organisms than ciprofloxacin, sparfloxacin, levofloxacin, ofloxacin, lomefloxacin and norfloxacin. In particular, it possesses very good *in vitro* activity against *Streptococcus pneumoniae* and better activity than ciprofloxacin against *S. aureus*, *S. pyogenes* and enterococci. It has greater activity against *S. pneumoniae* than sparfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, levofloxacin and grepafloxacin and activity comparable to or slightly less than the investigational agents clinafloxacin and DU-6859a. Trovafloxacin had greater activity against enterococci than ciprofloxacin, levofloxacin, ofloxacin and amoxicillin-clavulanate, however, resistance has been apparent. Some activity against vancomycin-resistant enterococci, similar to that reported with ofloxacin, sparfloxacin and clinafloxacin, has also been demonstrated. Trovafloxacin has greater activity than ciprofloxacin and oxacillin against methicillin-susceptible *S. aureus*. Against methicillin-susceptible and methicillin-resistant strains of *S. aureus* and *S. epidermidis*, trovafloxacin has activity greater than ciprofloxacin, comparable to vancomycin and slightly less than dalfopristin-quinupristin. Whether the enhanced *in vitro* activity against enterococci and methicillin-resistant strains of *S. aureus* and *S. epidermidis* translates into expanded clinical efficacy has yet to be determined.

Against most gram-negative organisms, trovafloxacin has slightly less activity than clinafloxacin, activity comparable to or slightly less than that of ciprofloxacin, activity comparable to sparfloxacin and levofloxacin and activity greater than that of ofloxacin, lomefloxacin and norfloxacin. Very good activity against *N. gonorrhea* and most of the common respiratory pathogens has been demonstrated. Against *Chlamydia* spp., trovafloxacin was 8 to 32 times more active than ciprofloxacin but slightly more active to similar in activity as ofloxacin. Against *C. pneumoniae*, trovafloxacin demonstrated activity similar or better than ofloxacin, but was less than that of doxycycline, erythromycin and azithromycin. Trovafloxacin is highly active against *Mycoplasma* spp. with greater activity than ciprofloxacin and ofloxacin and activity comparable to sparfloxacin.

Trovafloxacin has very good activity against anaerobic organisms. Trovafloxacin demonstrated greater activity against *B. fragilis* than sparfloxacin, levofloxacin, ciprofloxacin, grepafloxacin, cefoxitin and metronidazole. Good activity was also reported against non-fragilis *Bacteroides* spp., *Peptostreptococcus* spp., *Clostridium perfringens*, *Prevotella* spp. and *Fusobacterium* spp. In general, trovafloxacin has greater activity than other fluoroquinolones and clindamycin, ampicillin/sulbactam, cefoxitin and cefotetan, similar or slightly greater activity than metronidazole and slightly less activity than imipenem.

Trovafloxacin may also prove active against *Toxoplasma gondii*. Trovafloxacin appears to be poorly active against mycobacterial strains, with activity less than that of ciprofloxacin.

PHARMACOKINETICS: Trovafloxacin is well absorbed following oral administration, with a mean oral bioavailability of 88%. Peak levels are reached approximately 1 to 2 hours after oral administration. Time to peak is delayed, but the extent of absorption is not affected when trovafloxacin is administered with food. Administration of crushed tablets via a nasogastric tube to the stomach did not alter overall systemic exposure, and administration with concurrent enteral fluids did not affect absorption. Administration via a nasogastric tube to the duodenum resulted in a 30% reduction in systemic exposure. As with the other fluoroquinolones, concurrent administration with some cations (aluminum- and magnesium-containing antacids, iron salts, sucralfate) results in reduced trovafloxacin bioavailability.

The mean peak concentration was 2.2 mg/L and the AUC was 30.4 mg h/L following the oral administration of trovafloxacin 200 mg. After infusion of alatrofloxacin 200 mg, the mean peak concentration was 3.2 mg/L and the AUC was 34.7 mg h/L. Following single oral doses of 100 mg and 300 mg, peak concentrations of 1 mg/L and 2.9 mg/L were detected. Following daily dosing of 100 mg and 300 mg for 14 days, peak concentrations of 1.1 mg/L and 3.3 mg/L, respectively, were detected. In another study, single oral doses of 30 mg, 100 mg, 300 mg, 600 mg and 1000 mg produced peak plasma concentrations of 0.3 mg/L, 1.5 mg/L, 4.4 mg/L, 6.6 mg/L and 10.1 mg/L, respectively. Single intravenous doses of alatrofloxacin equivalent to trovafloxacin 30 mg, 100 mg, 200 mg and 300 mg resulted in peak plasma concentrations of 0.4 mg/L, 1.8 mg/L, 2.3 mg/L and 4.3 mg/L.

The mean half-life of trovafloxacin is 9 to 12 hours. Less than 10% of the administered trovafloxacin dose is recovered unchanged in the urine. Elimination is primarily via biliary excretion, with 43% of the dose excreted unchanged in the feces. Trovafloxacin is metabolized via conjugation. The major metabolites are an ester glucuronide, N-acetyl derivative and an N-acetyl

ester glucuronide. The N-acetyl trovafloxacin demonstrates some *in vitro* activity, but is 10-fold less active than trovafloxacin. Trovafloxacin is approximately 76% plasma protein bound.

In comparison to some of the older quinolones, trovafloxacin has a longer half-life, higher protein binding and reduced renal clearance. Some pharmacokinetic parameters are compared in Table 2.

Table 2: Comparative Pharmacokinetics of the Quinolones

Parameter	Cipro.	Grepa.	Levo.	Lome.	Oflox.	Spar.	Trova.
Half-life	4-6 h	15 h	6-8 h	7-8 h	4-5 h	20 h	9-12 h
Protein binding	20% - 40%	50%	24% - 38%	10%	32%	45%	76%
% excreted in urine unchanged	40% - 70%	<10%	87%	65%	65% - 80%	10%	5% - 10%

In patients with mild-to-moderate cirrhosis, trovafloxacin's AUC is increased 45% to 50%, and the half-life is increased by 25% to 30%. Dosage adjustments are recommended in patients with mild-to-moderate cirrhosis. There are no data on the pharmacokinetics of trovafloxacin in patients with severe cirrhosis; while no adjustment in dose may be necessary in patients with hepatic impairment from other causes. Pharmacokinetics do not appear to be altered in patients with renal dysfunction, including patients on hemodialysis. Therefore, dosage adjustments are not recommended in this population.

At this time, trovafloxacin is not indicated for use in infants or children; however, preliminary efficacy studies have been performed in children with meningitis, and a pharmacokinetic study in healthy children has suggested the pharmacokinetics of trovafloxacin following administration as alatrofloxacin do not differ from those in adults.

COMPARATIVE EFFICACY: Most trovafloxacin efficacy data were presented in the form of summaries in review articles and the package insert and in data presented in abstracts.

Community-Acquired Pneumonia

Trovafloxacin was compared with ceftriaxone/cefpodoxime in a study enrolling 443 hospitalized patients with community-acquired pneumonia. Patients received either monotherapy with alatrofloxacin followed by oral trovafloxacin 200 mg once daily for 7 to 14 days or intravenous ceftriaxone 1 g once daily followed by oral cefpodoxime 400 mg twice daily with optional intravenous/oral

erythromycin for 7 to 14 days. Clinical cure or improvement was observed in 90% of the trovafloxacin-treated patients and 87% of the ceftriaxone-treated patients at the end of treatment and in 86% and 82%, respectively, on day 30. No differences between treatments were observed. The results of this study have been summarized with the results of another study in the package insert. In the other study, patients with community-acquired pneumonia requiring hospitalization were treated with alatrofloxacin followed by oral trovafloxacin 200 mg once daily for a total of 7 to 14 days or intravenous ciprofloxacin 400 mg twice daily plus ampicillin 500 mg four times daily followed by oral ciprofloxacin 500 mg twice daily plus amoxicillin 500 mg three times daily for a total of 7 to 14 days. In the combined results of these two studies, clinical cure or improvement was achieved in 90% of patients on trovafloxacin and 90% of patients receiving the comparator agents at the end of therapy and in 86% and 85% of patients, respectively, at the end of the study (day 30).

Trovafloxacin was compared with clarithromycin in 359 patients with community-acquired pneumonia not requiring hospitalization or initial intravenous therapy. Patients were treated with either trovafloxacin 200 mg once daily for 7 to 10 days or clarithromycin 500 mg twice daily for 7 to 10 days. Clinical cure or improvement was achieved in 96% of trovafloxacin-treated patients and 94% of clarithromycin-treated patients at the end of treatment and in 89% and 86%, respectively, at the end of the study (day 30). No differences between treatments were detected. In another study enrolling patients with acute, uncomplicated community-acquired pneumonia, trovafloxacin 200 mg once daily for 10 days was reported to be as effective as cefaclor 500 mg three times daily for 10 days.

The results of a subset of patients infected with *S. pneumoniae* who were enrolled in six studies evaluating trovafloxacin in patients with community-acquired pneumonia were summarized in an abstract. A total of 1,998 patients were enrolled in the studies. Four studies evaluated trovafloxacin 200 mg once daily for 7 to 10 days, while two evaluated intravenous to oral therapy with alatrofloxacin and trovafloxacin 200 mg once daily for 7 to 14 days. Comparative medications in these studies included ceftriaxone alone or with erythromycin, ciprofloxacin alone or with ampicillin/amoxicillin, clarithromycin, cefaclor, amoxicillin plus erythromycin and high dose amoxicillin (3 g). *S. pneumoniae* was isolated in 127 trovafloxacin-treated patients and 130 patients treated with comparative agents. Clinical efficacy at day 30 was achieved in 91% of trovafloxacin-treated *S. pneumoniae* patients and in 88% of patients with *S. pneumoniae* treated with a comparative agent. Among patients with penicillin-resistant *S. pneumoniae*, clinical efficacy at 30 days was achieved in 96% of trovafloxacin-treated patients compared to 73% of patients treated with comparative agents, although the number of patients was small.

Nosocomial Pneumonia

The efficacy of trovafloxacin in the treatment of nosocomial pneumonia was also evaluated in a study enrolling 267 patients. Patients were treated with alatrofloxacin 300 mg once daily followed by oral trovafloxacin 200 mg once daily for a total of 7 to 14 days or ciprofloxacin intravenous 400 mg twice daily then orally 750 mg twice daily with optional clindamycin or metronidazole (for suspected anaerobic infection) for 10 to 14 days. Aztreonam or vancomycin could be added to either treatment arm for documented *P. aeruginosa* or MRSA infection. Clinical cure or improvement was achieved in 77% of trovafloxacin-treated patients and 78% of ciprofloxacin-treated patients at the end of therapy, and in 69% and 68%, respectively, at day 30. No differences between therapies were detected.

Sinusitis

In patients with acute sinusitis, trovafloxacin 200 mg daily for 10 days resulted in 96% eradication of *S. pneumoniae* and *H. influenzae*, 100% eradication of *S. aureus* and 90% eradication of *M. catarrhalis*.

Complicated Intra-Abdominal Infections

Alatrofloxacin 300 mg once daily followed by trovafloxacin 200 mg once daily for up to 14 days was compared with intravenous imipenem/cilastatin 1 g every 8 hours followed by oral amoxicillin/clavulanic acid 500 mg three times daily for up to 14 days in the treatment of hospitalized patients with complicated intra-abdominal infections, including post-surgical infections. Clinical cure or improvement was achieved in 88% of alatrofloxacin/trovafloxacin-treated patients and 86% of imipenem- and amoxicillin-treated patients at the end of therapy and 83% and 84% of patients, respectively, at the end of the study (day 30).

Gonorrhea

Single oral doses of trovafloxacin 50 mg, 100 mg and 200 mg were evaluated in the treatment of uncomplicated gonorrhea in 39 patients (16 men and 23 women). All 31 evaluable patients were cured.

Chlamydia

Trovafloxacin 200 mg daily produced an eradication rate of 98% in 42 patients with *C. trachomatis* infection.

Urinary Tract Infections

Trovafloxacin 100 or 200 mg once daily for 1 week was reported to be as effective as ciprofloxacin 500 mg/day, with eradication rates greater than 93% with all three regimens.

Meningitis

Trovafloxacin is not FDA approved for use in children, but promising penetration into cerebral spinal fluid (even following oral administration) was reported, and preliminary studies evaluated trovafloxacin in the treatment of meningitis in children.

Trovafloxacin efficacy in the treatment of *N. meningitidis* meningitis was demonstrated in one study. During a meningococcal outbreak in Nigeria, 200 children with meningitis were randomized to treatment with either alatrofloxacin or trovafloxacin 3 mg/kg once daily intravenously or orally for 5 days or ceftriaxone 100 mg/kg once daily intramuscularly or intravenously for 5 days. Clinical cure was achieved in 90% of trovafloxacin-treated patients and 89% of ceftriaxone-treated patients. Pediatric studies evaluating the efficacy in trovafloxacin in *S. pneumoniae* and *H. influenzae* type B meningitis are anticipated.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:

Table 3: Contraindications of Available Fluoroquinolones

Contraindication	Cipro.	Grepa.	Levo.	Lome.	Oflox.	Spar.	Trova.
Hypersensitivity	X	X	X	X	X	X	X
Hepatic failure		X					
History of photosensitivity						X	
QTc prolongation		X				X	
Inability to avoid sun exposure				X		X	

Trovafloxacin shares the quinolone class warnings and precautions regarding use in pediatric populations, pregnant women, nursing women and patients with central nervous system disorders, and the class warnings regarding convulsions, increased intracranial pressure, psychosis, central nervous system stimulation, hypersensitivity reactions, pseudomembranous colitis, tendon ruptures and phototoxicity.

Liver function test elevations have been observed with prolonged therapy. Therefore, patients receiving trovafloxacin for 21 days or longer should undergo periodic assessment of hepatic function.

Trovafloxacin is categorized in Pregnancy Category C. Skeletal abnormalities have been observed in animal studies. Trovafloxacin is distributed into breast milk. Because of the potential for unknown effects from trovafloxacin in the nursing infant, trovafloxacin therapy is not recommended during nursing.

At this time trovafloxacin is also not indicated for use in pediatric patients. Several small preliminary studies have evaluated trovafloxacin in pediatric patients, however, safety has not been established. Trovafloxacin, like the other quinolones, caused arthropathy and osteochondrosis in juvenile animals.

ADVERSE REACTIONS: The most common side effects of trovafloxacin and alatrofloxacin have included dizziness, lightheadedness, nausea, headache, vomiting, vaginitis and diarrhea. Dizziness is generally mild, lasts for a few hours after a dose and often resolves with continued dosing. The incidence of dizziness may be reduced by taking trovafloxacin at bedtime or with food.

Mild phototoxicity has been reported, however, trovafloxacin appears to be associated with a low potential for phototoxicity. Phototoxicity was observed in less than 0.03% of patients in clinical trials. In comparative studies of the phototoxic potential of several of the fluoroquinolones, trovafloxacin was judged to have a lower phototoxic potential than either ciprofloxacin or lomefloxacin, although greater than placebo.

ECG abnormalities and cardiotoxicity have not been reported with trovafloxacin.

DRUG INTERACTIONS: Concurrent administration with aluminum- and magnesium-containing antacids, antacids containing citric acid buffered with sodium citrate, sucralfate and products containing iron salts results in reduced trovafloxacin bioavailability. Such products should be taken at least 2 hours before or 2 hours after taking trovafloxacin. Calcium carbonate and omeprazole slightly reduced trovafloxacin bioavailability, but the interaction is not believed to be clinically important. Alatrofloxacin should not be co-administered with any solutions containing multivalent cations, such as through the same intravenous line as magnesium.

Concomitant administration of intravenous morphine with oral trovafloxacin resulted in a 36% reduction in the trovafloxacin AUC and a 46% reduction in the trovafloxacin peak serum concentration. Intravenous morphine should be administered at least 2 hours after oral trovafloxacin in the fasted state and at least 4 hours after trovafloxacin is taken with food. Whether similar effects on trovafloxacin absorption occur with the other opiate analgesics is unknown.

Trovafloxacin does not affect theophylline clearance. No effect on warfarin pharmacokinetics or pharmacodynamics have been observed. Trovafloxacin also does not appear to interact with cimetidine, digoxin or cyclosporine.

RECOMMENDED MONITORING: Liver function tests should be performed periodically in patients receiving trovafloxacin for 21 days or longer.

DOSING: No dosage adjustment is necessary when switching from intravenous to oral administration. Trovafloxacin can be taken without regard to meals.

Table 4: Recommended Trovafloxacin and Alatrofloxacin Dosage

Indication	Dose	Duration
Nosocomial pneumonia	300 mg IV, followed by 200 mg oral	10-14 days
Community-acquired pneumonia	200 mg oral or 200 mg IV followed by 200 mg oral	7-14 days
Acute bacterial exacerbation of chronic bronchitis	100 mg oral	7-10 days
Acute sinusitis	200 mg oral	10 days
Complicated intra-abdominal infections	300 mg IV followed by 200 mg oral	7-14 days
Gynecologic and pelvic infections	300 mg IV followed by 200 mg oral	7-14 days
Surgical prophylaxis	200 mg IV or oral	single dose within 0.5-4 hours before surgery
Skin and skin structure infections, uncomplicated	100 mg oral	7-10 days
Skin and skin structure infections, complicated	200 mg oral or 200 mg IV followed by 200 mg oral	10-14 days
Uncomplicated urinary tract infections	100 mg oral	3 days
Chronic bacterial prostatitis	200 mg oral	28 days
Uncomplicated urethral gonorrhea in males; endocervical and rectal gonorrhea in females	100 mg oral	single dose
Cervicitis due to *Chlamydia trachomatis*	200 mg oral	5 days
Pelvic inflammatory disease	200 mg oral	14 days

Alatrofloxacin, following dilution to a final concentration of 1 to 2 mg/mL, should be administered by intravenous infusion over 60 minutes. Alatrofloxacin can be diluted with 5% Dextrose Injection, 0.45% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, 5% Dextrose and 0.2% Sodium Chloride Injection or Lactated Ringers and 5% Dextrose Injection. The resulting solutions are stable for up to 7 days when refrigerated or up to 3 days at room temperature stored in glass bottles or plastic (PVC-type) intravenous containers.

PRODUCT AVAILABILITY: Trovafloxacin and alatrofloxacin received FDA approval in December 1997. Trovafloxacin mesylate is available in 100 mg and 200 mg oral tablets. Alatrofloxacin mesylate is available as a solution equivalent to trovafloxacin 5 mg/mL in 40 mL (200 mg) and 60 mL (300 mg) single-use vials.

COST:	100 mg	$ 4.75/tab	AWP
	200 mg	$ 5.75/tab	AWP
	200 mg	$29.50/vial	AWP
	300 mg	$44.50/vial	AWP

CONCLUSION: Trovafloxacin is a broad spectrum fluoroquinolone antimicrobial with good gram-negative coverage and enhanced gram-positive and anaerobic activity compared to the older quinolones. It also has a very good safety profile (minimal phototoxicity, few drug interactions and a lack of cardiotoxicity), is administered once daily and is available in oral and intravenous formulations that are dosed equivalently. Whether the enhanced gram-positive spectrum will translate into improved clinical efficacy has not been demonstrated; however, enhanced anaerobic activity does allow monotherapy with this agent when combination therapy has been required with other fluoroquinolones. Trovafloxacin is a welcome addition to this class of agents; however, cost will likely determine to what extent it is used. For many infections no advantage over ciprofloxacin, ofloxacin or levofloxacin is readily apparent. The improved safety profile makes use of this agent appear preferable to sparfloxacin and grepafloxacin.

Appendix
Comparative MIC90 Data

Organism	Trova	Cipro	Levo	Oflox	Spar
S. pneumoniae	0.25	4	2	4	0.5
	0.12	2	1	4	0.5
	0.12	2	1	2	0.25
S. aureus methicillin-sensitive	0.03	0.5	0.25		0.12
	0.015	0.5	0.25	0.5	0.06
	0.06	1	0.5	1	0.12
	0.06	1		0.5	0.125
S. aureus methicillin-resistant	1	64	8		8
	2	64		32	
	1	>16	8	16	8
	8	≥32	16	≥32	16
E. faecalis	0.25	2	2		1
	0.5	2		8	1
	0.5	4			1
	2	8		8	
	2	1	2	4	0.5
K. pneumoniae	0.5	0.25			0.5
	0.12	0.06	0.5	1	0.12
	2	2	2	4	1
P. aeruginosa	1	0.5	1		2
	8	16	8	>16	8
	4	1	8	16	8
	2	4	2	4	2
N. gonorrhoeae	0.004	0.015	0.015		0.004
	0.003	0.007			0.0015
	0.015	0.008		0.03	
M. catarrhalis	0.008	0.03	0.06		0.008
	0.03	0.06		0.12	
	0.03	0.12	0.12	0.12	0.03
H. influenzae	0.008	0.015	0.03		0.004
	0.015	0.12			0.015
	0.015	0.0145		0.03	
	0.03	0.03	0.03	0.06	0.015
B. fragilis	0.25	2	1		1
	0.5	32		16	
	2	64		64	
	1	16		8	

Community-Acquired Pneumonia in Adults: Guidelines for Management

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CID 1998;26 (April)

Table 12. Empirical antibiotic selection for patients with community-acquired pneumonia.

- Outpatients
  - Generally preferred: Macrolides,* fluoroquinolones,† or doxycycline
  - Modifying factors
    - Suspected penicillin-resistant *Streptococcus pneumoniae*: fluoroquinolones†
    - Suspected aspiration: amoxicillin/clavulanate
    - Young adult (>17–40 y): doxycycline
- Hospitalized patients
  - General medical ward
    - Generally preferred: β-lactam‡ with or without a macrolide* *or* a fluoroquinolone† (alone)
    - Alternatives: cefuroxime with or without a macrolide* or azithromycin (alone)
  - Hospitalized in the intensive care unit for serious pneumonia
    - Generally preferred: erythromycin, azithromycin, or a fluoroquinolone† *plus* cefotaxime, ceftriaxone, or a β-lactam–β-lactamase inhibitor§
  - Modifying factors
    - Structural disease of the lung: antipseudomonal penicillin, a carbapenem, or cefepime plus a macrolide* or a fluoroquinolone† plus an aminoglycoside
    - Penicillin allergy: a fluoroquinolone† with or without clindamycin
    - Suspected aspiration: a fluoroquinolone plus either clindamycin or metronidazole or a β-lactam–β-lactamase inhibitor§ (alone)

* Azithromycin, clarithromycin, or erythromycin.

† Levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, or another fluoroquinolone with enhanced activity against *S. pneumoniae*.

‡ Cefotaxime, ceftriaxone, or a β-lactam–β-lactamase inhibitor.

§ Ampicillin/sulbactam, or ticarcillin/clavulanate, or piperacillin tazobactam (for structural disease of the lung, ticarcillin/clavulanate or piperacillin).

CEFDINIR – Omnicef by Parke Davis (1-S)

INDICATIONS: Cefdinir is approved for the treatment of mild-to-moderate bacterial infections caused by susceptible strains of the designated microorganisms

Table 1: FDA-Approved Conditions and Susceptible Microorganisms for Cefdinir:

Bacterial Infection	Causative Organism*	Age Group
Community-acquired pneumonia Chronic bronchitis, acute exacerbation	*Haemophilus influenzae*, including beta-lactamase producing strains *Haemophilus parainfluenza*, including beta-lactamase producing strains *Streptococcus pneumoniae*, penicillin-susceptible strains only *Moraxella catarrhalis*, including beta-lactamase producing strains	Adolescents Adults
Pharyngitis Tonsillitis	*Streptococcus pyogenes*	Pediatrics Adolescents Adults
Skin and skin structure, uncomplicated	*Staphylococcus aureus*, including beta-lactamase producing strains *Streptococcus pyogenes*	Pediatrics Adolescents Adults
Maxillary sinusitis, acute	*Haemophilus influenzae*, including beta-lactamase producing strains *Streptococcus pneumoniae*, penicillin-susceptible strains only *Moraxella catarrhalis*, including beta-lactamase producing strains	Adolescents Adults
Otitis media, acute bacterial	*Haemophilus influenzae*, including beta-lactamase producing strains *Streptococcus pneumoniae*, penicillin-susceptible strains only *Moraxella catarrhalis*, including beta-lactamase producing strains	Pediatrics

= caused by susceptible strains of bacteria

CLINICAL PHARMACOLOGY: Cefdinir is a semisynthetic bactericidal third-generation oral aminothiazole oximino acid cephalosporin.
The minimum inhibitory concentration (MIC) for most susceptible organisms is ≤ 1 mcg/mL. A MIC of 2 mcg/mL is classified as intermediate sensitivity and ≥ 4 mcg/mL is resistant to cefdinir therapy. Post-antibiotic effects have been demonstrated against *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *E. coli*, *K. pneumoniae*, *H. influenzae* and *M. catarrhalis*, while other investigations have not shown any post-antibiotic effects with *E. coli* or *K. pneumoniae*.

Table 2 MIC 90 Data for Cefdinir

Organism	# Isolates	MIC 90 (ug/ml)
Staphyloccus aureus	261	0.03 – 1.0
Staphyloccus coag neg, ox sens	34	0.25 – 2.0
Staphyloccus coag neg. ox resis	35	>8 - >64
Staphyloccus aureus meth resis	88	>32 - >128
Streptococcus pneumoniae	381	<0.06 – 0.5
Streptococcus pyogenes	295	0.008 –0.015
Enterococcus faecalis, gent sens	30	16 - >16
Enterococcus faecalis, gent resis	16	32
H. influenzae, beta-lactamase pos	218	0.25 – 1.0
H. influenzae, beta-lactamase neg	238	0.25 – 1.0
M. catarrhalis	108	0.125 – 0.5
E. coli	1502	0.5 – 4.0
K. pneuminiae	698	0.25 – 2.0
P. mirabilis	386	0.06 – 2.0
P. vulgaris	67	2.0 – 8
P. aeruginosa	792	>4.0 - >64

MIC of 1.0 ug/ml or less is susceptible
MIC of 2.0 ug/ml is intermediate
MIC of 4.0 ug/ml or greater is resistant

PHARMACOKINETICS: Peak plasma concentrations occur 2 to 4 hours after oral administration of the capsule and suspension. The bioavailability of cefdinir is 21% following oral administration of the 300 mg capsule. If two 300 mg capsules are given at the same time, the bioavailability is decreased to 16%, while bioavailability of the suspension is 25%. Peak concentrations occur within 3 hours with the capsule in adults and 2.2 hours with the suspension in pediatric patients. Administration of the capsule with food causes the peak plasma concentration to decrease by 16% and the extent of absorption to decrease by 10%. Administration with a high-fat meal produces similar results. Therefore, the manufacturer has concluded the drug can be administered without regard to food.

Data on penetration into the cerebrospinal fluid are unavailable. Protein binding of cefdinir is 60% to 70%.The elimination half-life of cefdinir is 1.7 hours in patients with normal renal function. The primary route of elimination is by renal excretion. The amount of unchanged drug excreted in the urine is 11.6% to 18.4% of the administered dose. The half-life is increased by 2- to 5-fold in patients with renal dysfunction.

ADVERSE REACTIONS: The most frequent adverse reactions associated with cefdinir therapy are gastrointestinal (eg, diarrhea, nausea - see Tables 7 and 8). Most adverse effects are mild and self-limiting. Other reported adverse effects include rash, vaginal moniliasis, headache, abdominal pain, vaginitis and hypersensitivity reactions. The product labeling should be consulted for a complete list of the adverse effects reported with cefdinir. The incidence and type of adverse effects reported with cefdinir appear to be similar to those reported with other oral cephalosporins.

Table 3: Most Common Adverse Effects Reported with Cefdinir Capsules in Adult and Adolescent Patients (n=3275)

Adverse Effect	Incidence
Diarrhea	16%
Vaginal moniliasis	5%
Nausea	3%
Headache	2%
Abdominal pain	1%
Vaginitis	1%
Rash	0.9%
Dyspepsia	0.8%
Flatulence	0.6%
Vomiting	0.6%

Table 4: Most Common Adverse Effects Reported with Cefdinir Suspension in Pediatric Patients (n=1387)

Adverse Effect	Incidence
Diarrhea	8%
Rash	3%
Cutaneous moniliasis	1%
Vomiting	1%
Abdominal pain	0.9%

DRUG INTERACTIONS: Probenecid can inhibit the renal tubular excretion of cefdinir, resulting in a 54% increase in peak cefdinir concentration and 50% increase in its elimination half-life.

The oral absorption of cefdinir may be impaired if it is administered with antacids or iron. Concomitant administration with 30 mL of *Maalox TC* suspension produces a 40% decrease in the rate and extent of absorption. Concomitant administration with iron supplements can also decrease the rate and extent of cefdinir absorption. These drug interactions can be avoided by separating the time of administration of these agents by 2 hours. If the patient is an infant requiring iron-fortified infant formula, the drug and formula can be administered at the same time.

A positive direct Coombs' test has occurred with other cephalosporins and may occur with cefdinir. Cefdinir therapy can produce a false-positive urine test for ketones if the test uses the nitroprusside method. It has no effect on the tests that use nitroferricyanide. False-positive urine glucose tests can occur with Clinitest, Benedict's solution and Fehling's solution, while no false results are produced with the Clinistix and TesTape tests.

DOSING: The average dose of cefdinir for adolescents and adults is 600 mg/day as a single dose or two divided doses without regard to meals for 10 days. Once-daily administration has been documented to be equally effective as 300 mg twice daily. However, if the patient has a community-acquired pneumonia or skin infection, the drug should be given twice daily since once-daily administration has not been evaluated in these conditions. The dose should be decreased to 300 mg once daily if the patient's creatinine clearance is < 30 mL/min.

The pediatric dose is 14 mg/kg, up to a maximum dose of 600 mg/day, for 10 days. Once-daily administration can be used in most infections except skin infections. The dose should be decreased to 7 mg/kg (up to 300 mg) once daily in pediatric patients whose creatinine clearance is < 30 mL/min/1.73 m^2.

Table 5: Dosing of Oral Cefdinir in Adolescent and Adult Patients:

Infection	Dose	Frequency	Duration (days)
Community-acquired pneumonia	300 mg	q12h	10 days
Chronic bronchitis, acute exacerbation	300 mg 600 mg	q12h q24h	10 days
Maxillary sinusitis, acute	300 mg 600 mg	q12h q24h	10 days
Pharyngitis/tonsillitis	300 mg 600 mg	q12h q24h	5-10 days 10 days
Skin and skin structure infections, uncomplicated	300 mg	q12h	10 days

Table 6: Dosing of Oral Cefdinir in Pediatric Patients:

Infection	Dose	Frequency	Duration (days)
Otitis media, acute bacterial	7 mg/kg 14 mg/kg	q12h q24h	10 days
Maxillary sinusitis, acute	7 mg/kg 14 mg/kg	q12h q24h	10 days
Pharyngitis/tonsillitis	7 mg/kg 14 mg/kg	q12h q24h	5-10 days 10 days
Skin and skin structure infections, uncomplicated	7 mg/kg	q12h	10 days

PRODUCT AVAILABILITY: Cefdinir was approved by the FDA in December 1997. Cefdinir is available as a 300 mg capsule and 125 mg/5 mL strawberry flavored suspension. The capsules come in bottles of 60. The suspension is available in 60 mL and 100 mL bottles.[1] *Note:* The suspension contains 2.86 grams of sucrose per teaspoon, which may be a problem for patients with diabetes. The product should be stored at room temperature (25 C). The reconstituted suspension can also be stored at room temperature and does not require refrigeration.

COST: 300 mg tabs $3.36/cap AWP

Table 7: Storage Recommendations for the Reconstituted Oral Suspension:

Generic	Trade Name	Room Temp	Refrigerated
Cefdinir	*Omnicef*	10 days	Not Required
Cefixime	*Suprax*	14 days	14 days
Cefpodoxime proxetil	*Vantin*		14 days
Ceftibuten	*Cedax*		14 days

CONCLUSION: Cefdinir is an oral third-generation cephalosporin. It is effective against both gram-positive and gram-negative organisms. It has good *in vitro* activity against gram-positive and gram-negative organisms covered by other oral cephalosporins. It appears to offer no major advantages over cefixime, cefpoxodime or ceftibuten.

Troglitazone - Rezulin® by Parke-Davis and Sankyo - A new class of agents for the management of Type II diabetes - an "insulin sensitizer." Currently approved for use in patients who are poorly controlled (ie HbA_{1c} > 8.5%) and currently on ≥ 30 units of insulin per day. Requires endogenous insulin to work. Typically reduces HbA1c levels by ~ 1-1.5% and allows insulin dosage to be reduced by ~ 15-60%.

T½β 16-34 hours, hepatically metabolized to at least three metabolites which are largely excreted in the feces. Less than 3% eliminated in the urine, thus no dosage reduction in patients with renal dysfunction. Generally well tolerated.

Approximately 2.2% of patients experience elevated liver function tests (≥ 3 x's upper limit of normal). May also cause expanded plasma volume (↓ Hbg ~ 3-4% of patients). Has been reported to produce vascular tumors and LVH in rodents on high doses, not reported to date in humans or other animals. Being evaluated in patients with CHF. May ↑ HDL and LDL, ratio unchanged. Appears to stimulate cytochrome p450 III A4 (decreases terfenadine levels by 50-70% and also reduces both estrogen and progestin levels by ~ 30% when given to patients on oral contraceptives.

Pregnancy Category B

Indications

Troglitazone may be used concomitantly with a sulfonylurea or insulin to improve glycemic control. Monotherapy is indicated as an adjunct to diet and exercise to lower blood glucose in patients with Type 2 diabetes. Troglitazone should not be used as monotherapy in patients previously well controlled with a sulfonylurea alone, it should be **added** to, not substituted for, the sulfonylurea.

While not indicated, a recent abstract also suggests that the combination of troglitazone and metformin is also beneficial.

Clinical data - troglitazone added to baseline 12 mg micronized glyburide produces a dose related reduction in FBS and Hb A1c.

☞ Troglitazone monotherapy produced a dose related reduction in FBS and Hb A1c (decreased Hb A1c from 0.5 to 1.4%)
Usual dose 200-600 mg/day with meals (food enhances bioavailability by 30-85%).

200 mg	$2.48/tab AWP	(~ $ 74.00/mth)
400 mg	$3.95/tab AWP	(~ $119.00/mth)
600 mg	$4.96/tab AWP	(~ $149.00/mth)

UPDATE - 12/01/97 Changes in Patient Testing and Labeling

Following reports of 150 adverse events, including one liver transplant and three deaths in Japan, linked to liver failure. (An incidence of 0.02% among ~800,000 American and Japanese patients with diabetes treated with the drug since March 1997 - far below the anticipated 2.0% from clinical trials). The FDA states that they "continue to find the benefits outweigh the risks for treating appropriately selected and monitored Type 2 diabetes patients."

The labeling **NOW** reads - Liver enzymes and bilirubin levels be measured at the start of therapy and monthly for the first eight months, then every two months for the remainder of the first year of therapy, and periodically thereafter. In addition, LFT's should be done on any patient on troglitazone who develops symptoms of liver dysfunction (nausea, vomiting, fatigue, loss of appetite, dark urine, or jaundice).

UPDATE - 07/28/98

- Do not initiate therapy in patients with baseline ALT levels > 1.5 times the upper limit of normal (ULN).
- Recheck ALT weekly if levels between 1.5 - < 3 times ULN until normal, d/c if $\geq$ 3 times ULN.
- Limit use of 600 mg dose to 1 month if no response.

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Troglitazone Improves Glycemic Control In Patients with Type II Diabetes Who Are Not Optimally Controlled On Sulfonylurea.

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Type II diabetes is characterized by insulin resistance and an absolute or relative insulin secretory deficiency. In patients who are not optimally controlled on maximum doses of sulfonylurea (SU), the addition of troglitazone (T) to current SU therapy would improve insulin sensitivity, and maintain a level of stimulated insulin secretion, and potentially achieve a level of glycemic control not attainable by either medication alone. To test this hypothesis, 541 patients with type II diabetes, from 30 centers, uncontrolled on maximum doses of SU, (fasting serum glucose (FSG) ≥140 mg/dL and ≤300 mg/dL, C-peptide ≥1.5) were maintained for a 4 week baseline phase on 12 mg Glynase™ (G). At the end of baseline, patients with FSG > 140 mg/dL were equally randomized to seven blinded treatment arms: 12 mg G, 200 mg T, 400 mg T, 600 mg T, 12 mg G+200 mg T, 12 mg G+400 mg T, and 12 mg G+600 mg T. Baseline overall mean for FSG was 224.0 mg/dL and 9.6% for HbA_{1c}. Glycemic results after 52 weeks of treatment (intent-to-treat analysis) are summarized in the following table:

Adjusted Mean Difference From Glynase

	200T	400T	600T	G/200T	G/400T	G/600T
FSG (mg/dL)	19.6	-2.2	-11.6	**-53.7	**-60.8	**-79.1
HbA_{1c} (%)	*1.02	-0.05	0.03	**-1.60	**-1.81	**-2.65
Insulin (uIU/mL)	*-6.96	*-4.44	*-10.07	*-2.39	*-4.43	*-4.43

*p≤0.05. ** p≤0.0001 (Comparisons vs active control by Ancova with Rx, center, and baseline as covariates)

In addition, the percent of patient exhibiting an HbA_{1c} ≤ 7.9% were (6.3% G, 30.8% G/T200, 31.6% G/T400, and 57.5% G/T600). Adverse events and withdrawals due to adverse events were similar across all treatment arms. In conclusion, the addition of troglitazone to SU dramatically improved glycemic control in a patient population on the verge of insulin therapy. Combination therapy with troglitazone and SU provides a safe and effective approach for management of type II diabetes.

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Efficacy and Metabolic Effects of Troglitazone and Metformin NIDDM.

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We studied the effects of troglitazone (TGZ) and metformin (MET) monotherapy and in combination in 28 NIDDM subjects (16 women, men; mean baseline data: age 53, BMI 33.9 kg/m², fasting plasma gluco (FPG) 284 mg/dl, HbA1c 9.6%), equal in all parameters except for a slightly higher basal C-peptide in the TGZ group. After discontinuation of pri anti-diabetic therapy (mostly sulfonylureas) for 2 weeks, subjects were ra domized to either TGZ 400 mg QD or MET 1000 mg BID for 3 mont (mo.). Subsequently, the second drug was added for an additional 3 mo. A baseline, 3 and 6 mo., metabolic effects were assessed with FPG, HbA1c 8-hour meal tolerance test, and a 5-hour hyperinsulinemic (120 mU/m min) euglycemic clamp with di-deuterated glucose. No significant sid effects or adverse events were associated with combination therapy. After mo. of monotherapy, FPG decreased in both groups (TGZ: -17%, p=0.05 MET: -19%, p<0.001). HbA1c remained stable in both groups, compared t the HbA1c on prior therapy. Area under the curve for glucose during th meal tolerance test decreased by 56% in TGZ subjects (p=0.01) and 62% i the MET subjects (p<0.001). At 6 mo. (after 3 mo. of combined therapy) both groups experienced further and highly significant decreases in FBS (TGZ-MET: -42% (from baseline), p<0.001; MET-TGZ: -32%, p=0.001) At 6 mo., HbA1c had fallen 16% in the TGZ-MET group (p=0.03) and 13.2% in the MET-TGZ (p=0.05) group, compared to the HbA1c on prior therapy. Glucose infusion rates (GIR) during the clamp increased 43% in the TGZ subjects (p=0.04) and 20% in the MET subjects (p=0.03) at 3 mo. At 6 mo., GIR increased 108% and 55% in the TGZ-MET and the MET-TGZ groups, respectively (p=0.001 for both). SUMMARY: 1. MET and TGZ improve glycemic control in NIDDM to similar degrees. 2. Combined use of these agents is safe. 3. In combination, TGZ and MET have additive effects on FPG, HbA1c, and GIR.

MIGLITOL - GLYSET™ (Pharmacia & Upjohn) -1S

INDICATIONS: Miglitol is indicated as monotherapy, as an adjunct to diet, in the management of Type 2 diabetes mellitus. It is also indicated for use in combination with a sulfonylurea when diet plus either miglitol or a sulfonylurea alone does not result in glycemic control.

CLINICAL PHARMACOLOGY: Miglitol is a new alpha-glucosidase inhibitor that is structurally different from acarbose. Acarbose is a pseudotetrasaccharide, while miglitol is N-hydroxyethyl-1-desoxynojirimycin structurally similar to glucose. Despite the structural differences in these molecules, they are both effective alpha-glucosidase inhibitors.

In the small intestine, alpha glucosidases (eg, sucrase, maltase, glucoamylase, isomaltase) in the brush-border membrane are responsible for the digestion of complex polysaccharides and sucrose. Acarbose and miglitol are competitive inhibitors of the alpha-glucosidases. By inhibiting these enzymes, they are capable of delaying the digestion of complex carbohydrates (eg, starch) and the subsequent absorption of glucose, resulting in improved glucose control in some patients. In addition, mouth-to-cecum transit time is decreased resulting in less carbohydrate absorption and greater carbohydrate elimination in the stool. Acarbose is an irreversible competitive inhibitor of dextrinase, sucrase, isomaltase, glucoamylase and pancreatic amylase. Miglitol does not affect pancreatic amylase. The agents differ in their extent of inhibition of sucrase, glucoamylase and maltase; the affinity of miglitol for sucrase is six-fold greater than that of acarbose.

Miglitol is more potent than acarbose on a milligram-to-milligram basis. Despite systemic absorption, miglitol does not appear to exert clinically important extraintestinal effects. Miglitol has no effect on fasting blood glucose levels in patients with Type 2 diabetes. Its only effects on glucose are due to effects on glucose absorption.

Miglitol has no effect on *de novo* glycosylation of proteins, secretion of alpha$_1$-antitrypsin and alpha$_1$-acid glycoprotein. It does partly inhibit the formation of complex-type oligosaccharides by inhibiting glucosidases which result in the production of alpha$_1$-antitrypsin and alpha $_1$-acid glycoprotein that carry a mixture of both high-mannose and complex-type oligosaccharide side chains. However, this effect is only seen at high doses and is quickly reversible. The importance of these effects in clinical practice has not been determined.

PHARMACOKINETICS: Miglitol is rapidly absorbed following oral administration, reaching peak concentrations within 2 to 3 hours. The absorption of miglitol is saturable at high doses. A 25 mg dose is completely absorbed, but a 100 mg dose is only 50% to 70% absorbed.

Miglitol is distributed primarily in the extracellular space; the volume of distribution is low (0.18 L/kg). Protein binding is negligible (<4%).

Miglitol is renally eliminated unchanged; no metabolites have been detected in plasma, urine or feces. Over 95% of the dose is recovered in the urine within 24 hours following a 25 mg dose. While 61% of the dose was excreted in the urine unchanged following a 100 mg oral dose, reflecting the extent of absorption at that dosage. The elimination half-life is approximately 2 hours.

Miglitol accumulation is expected in patients with renal impairment. Patients with a creatinine clearance less than 25 mL/min taking miglitol 25 mg three times daily had miglitol plasma levels two-fold greater than patients with creatinine clearance greater than 60 mL/min. Dosage adjustments are not feasible since miglitol acts locally in the gastrointestinal tract. The safety of miglitol in patients with severe renal impairment has not been established. Miglitol pharmacokinetics are not altered in patients with hepatic impairment or in the elderly.

Acarbose is poorly absorbed from the gastrointestinal tract. Its systemic bioavailability is 1% to 2%. Despite its poor oral bioavailability, acarbose's efficacy is not altered since the majority of its beneficial effects are related to activity within the gastrointestinal tract. The remainder of acarbose appears to be metabolized by digestive enzymes or microorganisms in the gastrointestinal tract. Approximately 30% of

the dose is ultimately absorbed as metabolites and excreted in the urine.

CLINICAL EFFICACY: Single-dose and short-term studies conducted in small numbers of diabetic patients established miglitol as an effective adjunctive agent in the management of diabetes mellitus. These results indicate that miglitol is capable of suppressing postprandial blood glucose concentrations and decreasing the glucose AUC. One of these studies found 1-hour postprandial blood glucose levels after breakfast increased 23 mg/dL, after lunch increased 24 mg/dL and after dinner decreased 69 mg/dL, while the patient was receiving miglitol 100 mg twice daily. These values were increased by 92 mg/dL, 15 mg/dL and 2.5 mg/dL, respectively, during the placebo phase of the study. Postprandial C-peptide and insulin levels were reduced after breakfast and dinner and unaffected after lunch when the patient was receiving miglitol therapy. In addition, it was demonstrated that the beneficial effects on postprandial blood glucose levels were not dependent on the amount of carbohydrate in the diet.

Therefore, no special recommendations regarding the carbohydrate composition of meals are required to maintain miglitol beneficial effects. Nor does tolerance to the alpha-glucosidase inhibition or its effects on carbohydrate absorption develop in studies lasting up to 14 weeks. Several studies lasting 6 months to 1 year demonstrated that miglitol therapy resulted in greater reductions or smaller increases in HbA_{1C} than placebo therapy and further reductions in HbA_{1C} in patients receiving a sulfonylurea, indicating long-term effects on glycemic control.

One hundred and ninety-two patients with Type 2 diabetes mellitus, who had inadequate metabolic responses to maximum doses of an oral sulfonylurea, were enrolled in a double-blind, placebo controlled multicenter miglitol trial. These patients had to have been treated with an oral sulfonylurea at maximal recommended daily doses for at least 28 days and have an HbA_{1C} of 6.5% to 12% and a fasting plasma glucose level of greater than 140 mg/dL, but not greater than 250 mg/dL. At baseline, the mean body mass indexes and diet variables were comparable in all three groups. Prior to randomization, all eligible patients went through a 6-week, single-blinded run-in phase where they were given a placebo three times daily. Previous oral sulfonylurea therapy was continued unaltered throughout the study and patients were instructed to follow a standard, weight-maintaining diabetic diet. Patients were then randomly assigned to treatment with placebo (n = 63), miglitol 50 mg (n = 61) or miglitol 100 mg (n = 68). Patients were instructed to take the study medication three times daily with the first bite of each main meal. Patients randomized to the miglitol 100 mg were first treated with 50 mg miglitol three times daily for 2 weeks prior to the final dosage increase. If hypoglycemia occurred, the dose of the oral sulfonylurea may have been reduced. Postprandial plasma glucose and HbA_{1C} determinations were done several times throughout the study. Baseline HbA_{1C} values were 8.87% with placebo, 8.76% with miglitol 50 mg and 8.91% miglitol 100 mg; with the normal range being 4% to 6%. The results of this study are described in Table 1, Table 2 and Figure 1. Long-term efficacy was also reported with the addition of miglitol therapy in patients with Type 2 diabetes treated with insulin. The addition of placebo or miglitol 100 mg three times daily for 24 weeks was evaluated in 117 patients treated with insulin. Miglitol therapy resulted in a reduction in postprandial blood glucose and a 16% reduction HbA_{1C} compared to placebo.

Table 1: Laboratory Results in Type 2 Diabetes Mellitus, Who Had Inadequate Metabolic Responses to Maximum Doses of an Oral Sulfonylurea, Treated with Miglitol:

	Baseline			Change from Baseline During Double-Blind Treatment After 8 Weeks		
Laboratory Parameters	Placebo	Miglitol 50 mg	Miglitol 100 mg	Placebo	Miglitol 50 mg	Miglitol 100 mg
Fasting plasma glucose (mg/dL)	203	196	204	6	-12	-9
Plasma glucose AUC x 10^3 (mg*min^{-1}*dL^{-1})	39.6	38.6	39.7	0.3	-6.2	-7.5
Plasma glucose Cmax (mg/dL)	348	344	355	5	-62	-68
Fasting serum insulin (mcU/mL)	11.6	11	13.3	0.7	0.3	-0.7
Serum insulin AUC x 10^3 (mcU*min^{-1}*mL^{-1})	3.8	3.3	3.6	-0.1	-0.6	-0.7
Serum insulin Cmax (mcU/mL)	40.1	40.2	37.5	2.1	-8.8	-4.9
Fasting triglycerides (mg/dL)	222	201	202	27	-20	-18

AUC = area under the curve
Cmax = maximum concentration

Table 2: Laboratory Results in Type 2 Diabetes Mellitus, Who Had Inadequate Metabolic Responses to Maximum Doses of an Oral Sulfonylurea, Treated with Miglitol:

	Change from Baseline During Double-Blind Treatment					
	After 14 Weeks			At Double-Blind Endpoint		
Laboratory Parameter	Placebo	Miglitol 50 mg	Miglitol 100 mg	Placebo	Miglitol 50 mg	Miglitol 100 mg
Fasting plasma glucose (mg/dL)	7	-5	3	7	-10	-2
Plasma glucose AUC x 10^3 (mg*min^{-1}*dL^{-1})	-0.1	-5.7	-6.3	-0.4	-6.1	-6.3
Plasma glucose Cmax (mg/dL)	-1	-56	-63	-4	-61	-68
Fasting serum insulin (mcU/mL)	1.9	0.2	0.7	1.9	-0.3	-0.2
Serum insulin AUC x 10^3 (mcU*min^{-1}*mL^{-1})	0	-0.5	-0.8	-0.1	-0.6	-0.8
Serum insulin Cmax (mcU/mL)	-0.2	-8.2	-7.3	-0.3	-9.1	-8
Fasting triglycerides (mg/dL)	22	-19	-24	12	-30	-20

AUC = area under the curve
Cmax = maximum concentration